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OCULAR DRUG DELIVERY SYSTEM: A REVIEW ARTICLE

Yogesh H. Kadam,* Swapnil D. Deo, Harshal L. Tare
TSPM's, Trimurti Institute of Pharmacy Jalgaon, Maharashtra, India

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For Correspondence:

Yogesh H. Kadam

TSPM's, Trimurti
Institute of Pharmacy
Jalgaon, Maharashtra,
India

ABSTRACT

Eye is the organ of human body having main function of vision. Ocular drug delivery system is one of the most interesting and challenging task for pharmaceutical researchers. For a prolonged duration the major barrier in ocular medication are the ability to maintain therapeutic level of drug at the site of action. Ocular drug delivery is the alternative route for the systemic treatment of disease and also route for treatment of eye disease conjunctivitis. The purpose of this review giving a current knowledge in this field of ocular drug delivery. The ocular drug delivery has been major challenges to drug delivery scientist mainly due to its unique anatomy and physiology. One of the major problem encountered by the conventional ocular doses form include the rapid precorneal drug loss due to nasolacrimal drainage, tear turnover and drug dilution resulting in poor bioavailability.

INTRODUCTION

Eye is most interesting organ due to its drug disposition characteristics. Eye is the most easily accessible site for topical administration of medication. Drugs are commonly applied to the eye for localised action, on the surface, or in the interior of the eye. Generally topical application of drug is the method of choice under most circumstances because of its convenience and safety for ophthalmic chemotherapy. Novel therapeutic agents continue to provide ocular delivery systems with high therapeutic efficacy. Conventional ophthalmic formulations like solution, suspension and ointment have many disadvantages which result in low bioavailability of drug in ocular cavity. The various approaches that have been attempted to increase the bioavailability and the duration of the therapeutic action of ocular drugs can be divided into two categories. Ocular deposition and elimination of therapeutic agents is dependent upon its physicochemical properties as well as relevant ocular anatomy and physiology. The first one is based on the use of sustained drug delivery systems, which provide the control and continuous delivery of ophthalmic drugs. The second involves maximizing corneal drug absorption and minimizing precorneal drug loss. Ocular dosage forms are mainly affected by the precorneal loss factors which include tear dynamics, non-productive absorption, and transient residence time in the cul-de-sac.

The usefulness of this route of drug administration can be easily appreciated because the drug enters the systemic circulation circumventing the hepatic first pass effect. Ophthalmic drug delivery is the most interesting and challenging delivery system facing the pharmaceutical scientist. The anatomy, physiology and biochemistry of the eye render this organ highly impervious to foreign substances. A significant challenge to the formulator is to circumvent the protective barrier of the eye without causing permanent tissue damage. These barriers affect the bioavailability of drugs. In an ocular drug delivery system, there is a main problem of rapid and extensive elimination of conventional eye drops from the eye. This problem results in extensive loss of drug. Only a few amounts of drug penetrate the corneal layer and reach the internal tissues of the eye.

Ideal properties:-

- It has good rheological properties
- It has a non-irritative form
- It is easy to install and remove.
- It shows good corneal penetration.
- Continued contact time between cornea and drug.

Anatomy and physiology of the eye:-

A. Sclera:- The sclera (white portion of the eye) is the tough white sheath that forms the outer-layer of the ball. It is a firm fibrous membrane that maintains the shape of the eye as an approximately globe shape. It is thicker towards the posterior aspect of the eye than towards the anterior of the eye.

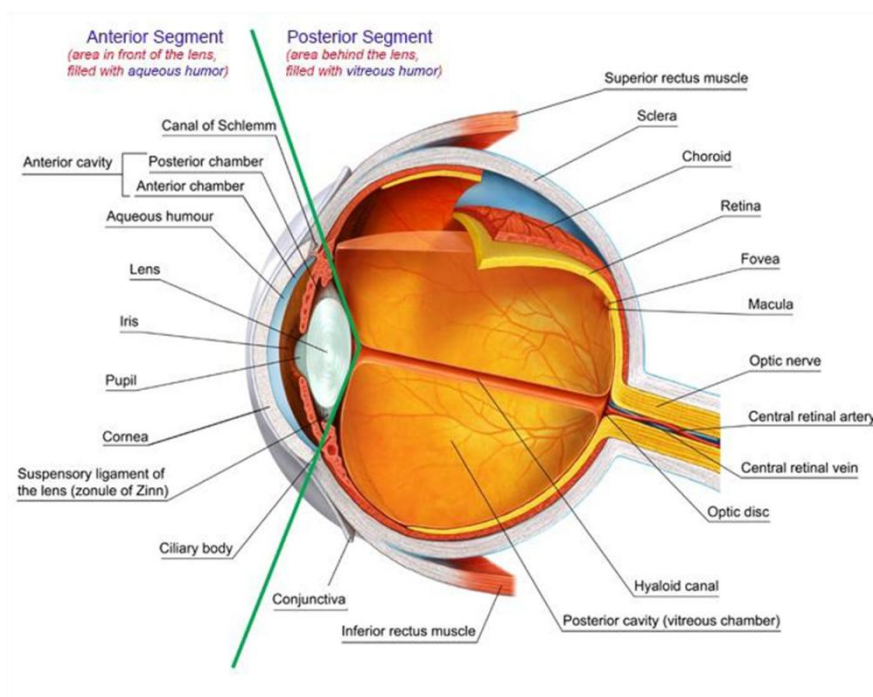
- B. The conjunctive:-** the conjunctiva is a thin transparent mucous epithelial barriers, lines the inside of eyelids, and covers the anterior one third of eyeball. The conjunctive is composed of two layers: an outer epithelium and underlying stroma. The exposed surface of the eye includes constructive and cornea and is covered with the tear film. the conjunctiva contributes the formation of CR film by way of security assistant electrolytes fluid and mucins.
- C. Cornea:-** the cornea is a strong clear bulge located at the front of the eye. Surface of the other cornea has a radius of approximately 8 mm. The cornea is non vascular structure. Get the necessary nutrients from the capillary that terminate looks at the circumference. It is supplied by many nerves derived from the ciliary nerves. These enter the laminated tissue of the cornea.
- D. Aqueous humour:-** the Aqueous humour is a jelly like substance located in the outer chamber of the eye. It is watery fluid that fills the “anterior chamber of the eye” which is located immediately behind the cornea in front of the lens. The aqueous humour is slightly alkaline solution that includes tiny quantities of sodium and chloride ions. Scleral venous sinus is a circular channel that collects aqueous humour from the anterior chamber and delivers it into bloodstream why the anterior ciliary veins. in human the rate of aqueous humour turnover is approximately 1% to 1.5% of anterior chamber per minute. Accuracy humour consists of pressure dependent and pressure independent pathway. The pressure dependent outflow refers to trabecular meshwork-schlemm's canal-venous system, while pressure independent or refers to any trabecular outflow and is called as uveoscleral outflow.
- E. Pupil:-** pupil generally appears to the dark” centre” of the eye, but can be more accurately described as the circular aperture in the centre of iris through which light passes into the eye. The size of pupil is regulated by the pupillary reflex.
- F. Iris :-**the ridge is a theme circular contractile certain located in the front of lens but behind the cornea. It is coloured part of the eye.
- G. Ciliary muscle:-**the ciliary muscles is wearing striated smooth muscle in the eyes. The muscle has parasympathetic and sympathetic innervation. Contraction and relaxation of ciliary muscles alters the curvature of the lens. this process may be described simply as the balance existing at many times between two States: *ciliary muscles relaxed* and *ciliary muscle contracted*.
- H. Lens:-**the lens is a transparent structure included in thin transparent capsule. It is located behind pupils of the eye. The lens produces light into an image on the retina. These adjustments of the shape of the lens is called accommodation and is archived by the contraction and relaxation of ciliary muscles.
- I. Retina:-** the retina is located at the back of the human eyes. Retina may be described as the “screen” on which an image is formed by the light that has password into the eye by the cornea, Aqueous humour, pupils, lens and finally the vitreous humour before reaching the retina.
- J. Choroid:-**the choroid layer is located behind the retina and absorbs unused radiation and nurses the outer portion of the retina. It is thin , highly vascular membrane that is dark brown in colour and contains a pigment that absorbs excess light and prevents

blurred vision. The choroid has one of the highest blood flow in the body. The choroid is loosely attached to the inner surface of this sclera.

K. Vitreous humour:- the vitreous humour is located in the large area that occupies approximately 80% of space in human eye. The vitreous humour is perfectly transparent thin jelly like substance that fills the chamber behind the lens of the eyes.

L. Macula:- the centre of the retina is called the macula. The macula contains high concentration of photoreceptor cell which convert light into nerve signals.

M. Optic nerve:- the optic nerve is responsible for transmitting no signals from the eye to the brain. These nerve signals contains information on an image for processing by the brain. The front surface of optic nerve which is visible on the retina is called the optic disc.



Functions:-

1. The eye is the organ that works with the brain to provide us with the change of sight. It works much like a camera.
2. The main function of eye is to collect light and turn it into electric signals, which are sent to the brain.
3. If we lose the vision in one eye, we can continue to see most of what we could see before. When light enters the eye it first passes through the cornea.
4. The light then passes the pupil, where it adjusts the amount of light entering the eye.
5. The light then passes through the lens of the eye. The lens focuses light rays onto the retina where it is changed into a signal that is transmitted to the brain by the optic nerve.

Management of eye diseases:-

A. Conjunctivitis:- bacterial conjunctivitis is an inflammation of the conjunctiva caused by bacteria. Conjunctivitis is swelling or infection of the membrane lining the eyelids it is characterized by cellular infiltration and exudation.

Conjunctivitis can be classified as :-

1. Infective-Acute, Sub acute & chronic.
2. Allergic Conjunctivitis.

B. Corneal ulcers: - Inflammation of Cornea is characterized by corneal Oedema, cellular infiltration and ciliary congestion. Being the most anterior part of eyeball, cornea is exposed to atmosphere and hence prone to get infected easily. Bacterial Corneal ulcers are most commonly caused by virulent organism. Common bacteria associated with corneal ulceration are E.coli.

C. Endophthalmitis:- it is severe form of intraocular inflammation involving ocular cavities and inner coats of eyeball. Causative organism include E.coli, streptococci.

Accordingly, the armamentarium of available antimicrobial used in the prevention and treatment of these infections includes antiviral , antifungal, and antibacterial. Common topical antibacterial used in the treatment of ocular infectious disease include sulfonamides, aminoglycoside, and fluoroquinolones.

The fluoroquinolones represented an expanding class of broad antibacterial, which cover a host of gram-negative and anaerobic species responsible for ocular infection. These antibacterials have gained popularity in ophthalmology field change they have been should to be equivalent to combination therapy in treatment of many ocular infection. Fluoroquinolones are also effective *Streptococcal* and *Staphylococcal* species.

Advantages of ocular drug delivery system:-

- Increased accurate dosing, to overcome the side effect of pulsed dosing produced by conventional system.
- To provide sustained and controlled drug delivery.
- To increase the ocular bioavailability of drug by increasing the cornea contact time.
- This can be achieved by effective adherence to corneal surface.
- To provide targeting within the ocular globe so as to prevent the loss to order ocular tissue.

- To circumvent the protective barriers like drainage, lacrimation and conjunctive absorption.
- To provide comfort better compliance to the patient and to improve therapeutic performance of the drug.
- To provide better housing of delivery system.

Disadvantages of ocular drug delivery system:-

- The physiological restriction is the limited permeability of cornea resulting into low absorption of ophthalmic drugs.
- the major portion of administrative does drains into the lacrimal duct and thus can cause unwanted systemic side effects.
- the rapid elimination of drugs through the eye blinking and tears flow results in short duration of therapeutic effect resulting in frequent dosing regimen.
- The drug solution stays very short time in the eye surface.
- It shows poor bioavailability and instability of the dissolvable drug.

Method of preparation of ophthalmic drugs:-

Solvent casting method:- in this method using different ratio of drug and polymer and prepare number of batches. Firstly, in distilled water the polymer is dissolved. In stirring condition of plasticizer is added to this solution. The weight amount of the drug was added to the solution and stirred to get a uniform dispersion. After mixing this solution poured in petridish and covered with funnel to allow slow evaporation at room temperature for 48 hour. The dried films thus obtained then cut into circular pieces of definite size containing drug. The ocular inserts were Stored in desiccators under ambient condition.

Gelfoam disc:- A gelfoam disc which diameter is 0.4 mm and 0.5 mm thickness was punched from slab of gelfoam sponge with common hole punch and phenylephrine HCL 1.7 mg and tropicamide 0.6 were dissolved in a solution of 50%v/v ethanol in water. The solution was placed in gelfoam disc. Under vacuum for at least 72 hour, the weight Matrix where dried. By this method placed device where also prepared but without drug. The dose of phenylephrine and tropicamide are equal to two drops each of Mydriacy.

Mould preparation:- using amount of polymer, drug and excipients we prepared polymethylsiloxane rod-shaped silicone inserts. into the aluminium moulds the mixture where injected and where allowed to cure at 45°C for 24 hour. The resulting rubbery cylinders were appropriately cut to give a drug content of specific amount. The final length and

weight where in range 4 to 12 mm and 2.7 to 8.0 mg, depending on insert type. The rod shaped silicone insert were use, as such and after poly-acrylic acid or polymethacrylic acid coating, for hydration test and for in vitro and in Vivo drug release studies.

Evaluation parameter:-

Sterility test:- the insert where sterility using Gamma radiation before carrying out the irritancy and in Vivo drug release study. No microbial or fungal growth was seen in any of formulation, which indicate that the films were sterilize completely.

Surface pH determination:- the pH of solution, drop, suspension and in suit is most often determined using potentiometric method. In this method the pH value is determined by measuring potential difference between electrodes placed in examined and reference solution of known pH or between measurement electrode and reference electrode, both placed in examination preparation.

Clarity examination:- clarity examination involves the visual assessment of formulation in suitable lightning on white and black background. It is performed for liquid form with exception of suspensions. This examination applies to eye drops and in site gels before and after gelling.

Another method of clarity examination involves transmittance measurement using a UV-Vis spectrophotometer. This method can be employed in research on contact lenses field with active ingredients. The lenses are hydrated in physiological saline and placed on the surface of quartz cuvette. The transmittance is measured afterward from 200 to 1000 nm wavelength.

Physiological barriers of ODDS:-

Physiological barriers to diffusion and productive absorption of topically applied drug exist in precorneal and corneal spaces. The precorneal constraints such as tear dilution, solution drainage, lacrimation, tear turnover and conjunctive absorption are responsible for poor ocular bioavailability of conventional ophthalmic doses form. Drug solution drainage away from the precorneal area has been shown to be the most significant factor in reducing The contact time of the drug with the cornea and consequently ocular bioavailability of topical dosage form. The instilled dose leaves the precorneal area within 2 minutes of installation in humans. The ophthalmic dropper delivers 50-75 , of the eye drops. If the patient does not blink, the eye can hold about 30 without spilling on to the cheek.

Lacrimal fluid eye barriers:-

Corneal epithelium limit drug absorption from the lacrimal fluid into the eye. the corneal epithelial cells form tight junctions that limit the paracellular drug permeation. Therefore lipophilic drugs have topically at least an order of magnitude higher permeability in the cornea than hydrophilic drugs.

Blood ocular barriers:-

Why is protected from the xenobiotic in the bloodstream by blood ocular barriers. These barriers have two parts: blood aqueous barrier and blood retinal barrier.

The barrier prevents the access of plasma albumin into the eye and also limit the access of hydrophilic drug from the plasma into the aqueous humour. posterior barrier between bloodstream and eye is composed of retinal pigment epithelium and tight junctions of retinal capillaries.

Drug easily gain access to the choroidal extravascular space, but there after distribution into the retina is limited by the RPE and retinal endothelial.

Marketed Ophthalmic drug delivery product:-

- a. **Drug name:-** carbahol
Brand name:- Dichol
Dosage form:- Sterile solution
Use:- in ophthalmic Surgery
- b. **Drug name:-** Dexamethasone
Brand name:- Dexcin
Dosage form:- Eye drop
Use :- in eye infection
- c. **Drug name:-** Polymixin-B
Brand name:- Ocupol
Dosage form:- Eye drop
Use:- Corneal ulcer.
- d. **Drug name:-** Acyclovir
Brand name:- Acivir eye
Dosage form:- Ointment
Use :- Eye infection.
- e. **Drug name:-** Chloramphenicol palmitate.
Brand name:- Chlorine Erin

Dosage form :- Ointment

Use :- Conjunctivitis.

f. Drug name:- Ciprofloxacin.

Brand name:- Ciplox

Dosage form :-Eye drop

Use:- Conjunctivitis

g. Drug name:- Betamethasone.

Brand name:- Betnisol N

Dosage form:- Eye drop

Use:- Eye infection

h. Drug name:- Hydroxyproline methylcellulose.

Brand name:- Refresh tears

Dosage form:- Eye drop

Use :- Eye lubricant.

i. Drug name:- Timolol maleate.

Brand name:- Timolol de

Dosage form :- In-situ gel

Use :- Keratoconjunctivitis

CONCLUSION:

The reason of this review gives present information in this field of ocular drug delivery. The ocular drug delivery has been chief dispute to drug delivery scientist mostly due to its single anatomy and physiology. One of the main difficulty encountered by the conventional ocular doses form comprise the quick precorneal drug loss due to nasolacrimal drainage, tear turnover and drug dilution resulting in poor bioavailability.

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